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Review article

HDL-cholesterol as a marker of coronary heart disease risk: the Québec cardiovascular study

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Abstract

Background: Primary as well as secondary prevention trials have shown the relevance of lowering LDL-cholesterol to reduce coronary heart disease (CHD) risk. However, although the association between LDL-cholesterol and CHD is well recognized, there is a considerable overlap in the distribution of plasma LDL-cholesterol levels between CHD patients and healthy subjects. The objective of the present review article is to use data from the Québec cardiovascular study to demonstrate that in men, a low HDL-cholesterol may be even more of a risk factor and a target for therapy than a high LDL-cholesterol. *Methods and results:* Results of the Québec cardiovascular study, a prospective study of 2103 middle-aged men followed for a period of 5 years, have confirmed results of previous studies in showing that plasma HDL-cholesterol concentration was an independent predictor of a first ischemic heart disease (IHD) event which included typical effort angina, coronary insufficiency, nonfatal myocardial infarction and coronary death. In addition, a reduced plasma HDL-cholesterol concentration was found to have a greater impact than raised LDL-cholesterol on the atherogenic index (total cholesterol/HDL-cholesterol ratio), this ratio being the best variable of the traditional lipid profile for the prediction of IHD events in the Québec cardiovascular study. However, a low HDL-cholesterol concentration is not often observed as an isolated disorder but also includes hypertriglyceridemia, elevated apo B concentration, and an increased proportion of small, dense LDL particles. These abnormalities are features of an insulin resistant-hyperinsulinemic state resulting from abdominal obesity. *Conclusions:* It is therefore recommended that we need to go beyond LDL-cholesterol measurement lowering therapy for the optimal management of CHD risk. Raising plasma HDL-cholesterol through weight loss and a healthy diet, by an increased physical activity and, if required, by proper pharmacotherapy is therefore a legitimate therapeutic target for the optimal prevention of CHD in a large proportion of high risk patients.

Keywords: HDL-cholesterol; Triglycerides; Coronary heart disease; Abdominal obesity; Cholesterol/HDL-cholesterol ratio

1. Introduction

The relationship between plasma LDL-cholesterol and the risk of coronary heart disease (CHD) is very well established [1–4]. Furthermore, large randomized primary [5,6] and secondary [7–9] prevention trials have shown that reducing plasma LDL-cholesterol levels with the use of statins led to a reduction in the number of CHD events and to a decrease in CHD-related mortality rates. However, although the development of statins has been a remarkable breakthrough regarding our ability to significantly reduce plasma LDL-cholesterol levels and related CHD risk, it is important to recognize that the relative reduction in the number of CHD events achieved with hypolipidemic drugs has been approximately 30% [10]. Thus, CHD

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patients treated with statins do remain at a high absolute risk for a recurrent CHD event. Furthermore, there is a considerable overlap in the distribution of plasma LDL-cholesterol levels between CHD patients and healthy individuals. Fig. 1 shows the distribution of plasma LDL-cholesterol at baseline in middle-aged men of the Québec cardiovascular study. Although there was a highly significant difference in average plasma LDL-cholesterol levels between the 114 men who developed a first ischemic heart disease (IHD) event (typical effort angina, coronary insufficiency, nonfatal myocardial infarction and coronary death) over the 5-year follow-up period compared with the 1989 men who remained healthy. Indeed, a substantial proportion of patients who developed a first IHD event had plasma LDL-cholesterol concentrations below the average of men who remained IHD-free. Thus, our ability to identify high-risk patients solely on the basis of LDL-cholesterol may be limited [10].

Epidemiological research conducted over the last 40 years has allowed the identification of markers of CHD risk. It is now well established that additional risk factors, such as diabetes, hypertension and smoking substantially increase risk of CHD for any given level of LDL-cholesterol [2,11]. Furthermore, it is now common practice to measure HDL-cholesterol levels [12–15] and to compute the LDL-cholesterol/HDL-cholesterol or the cholesterol/HDL-cholesterol ratios for a better assessment of CHD risk [2,16–18]. Whether hypertriglyceridemia is an independent risk factor for CHD remains a matter of debate [19–25], but it is increasingly accepted that the presence of hypertriglyceridemia increases the likelihood of finding related atherothrombotic metabolic abnormalities [26,27]. It is also well known that a positive family history of early CHD increases risk even in the absence of any dyslipidemia [2,16–18]. More recently, new markers of risk have been proposed. They include apolipoprotein (apo) B [28] and elevated Lp(a) levels [29,30], the presence of

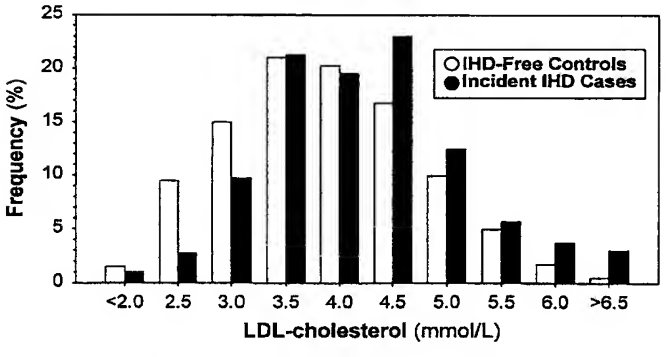

Fig. 1. Distribution of baseline plasma LDL-cholesterol levels in 114 men of the Québec cardiovascular study who developed IHD vs those ($n = 1989$) who remained IHD-free over a 5-year follow-up period.

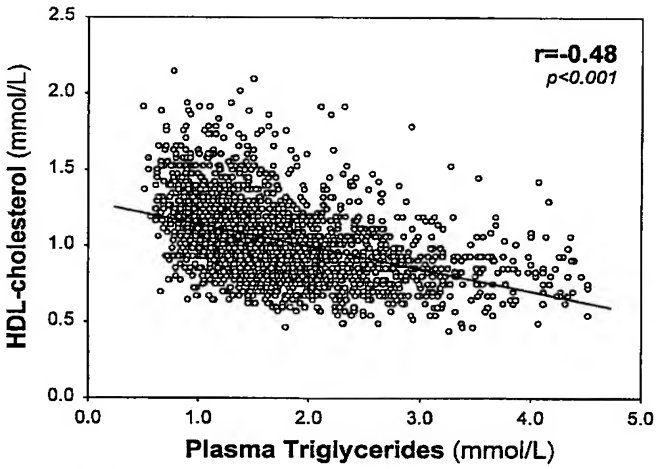

Fig. 2. Relationship between plasma HDL-cholesterol levels and triglyceride concentrations in the sample of 2103 men of the Québec cardiovascular study.

small, dense LDL particles [31–33], hyperinsulinemia as a marker of insulin resistance in non-diabetic subjects [34,35], elevated homocysteine concentrations [36,37], renin and aldosterone in hypertensive patients [38,39], markers of an impaired fibrinolytic capacity and of susceptibility to thrombosis [26,27,40,41] and markers of systemic inflammatory processes [42,43].

The objective of this review is to discuss work from our laboratory, which emphasizes the importance of HDL as a risk factor for CHD. Results from the prospective Québec cardiovascular study as well as data from our metabolic studies, which are relevant to our understanding of the low HDL syndrome, will be reviewed concurrently. As we have used cumulative IHD end points in the Québec cardiovascular study, we will refer to IHD when discussing our results whereas CHD will be used to globally describe events in other studies.

2. HDL-cholesterol, triglycerides and CHD risk

The relationship of a low HDL-cholesterol concentration to an increased risk of CHD has become a widely accepted concept. Early data from the Framingham study [12] have shown that low HDL-cholesterol concentration was associated with a substantial increase in the risk of CHD. In a review article on this topic, Austin examined 19 prospective studies with measurements of HDL-cholesterol levels and found that 15 studies reported evidence for a cardio-protective effect of HDL-cholesterol, 3 studies reported a trend for a favorable relationship, whereas only 1 study found no evidence for a significant association between HDL-cholesterol concentration and CHD risk [20]. Therefore, there is overwhelming evidence that low HDL-cholesterol concentrations are associated with an

increased risk of CHD. Fig. 2 illustrates a well-accepted phenomenon related to low HDL-cholesterol levels. Indeed, it is well known that there is a highly significant negative relationship between plasma HDL-cholesterol concentrations and fasting triglyceride levels. Although the shared variance only reaches 25%, subjects who have a low HDL-cholesterol concentration also tend to be characterized by hypertriglyceridemia. The extent to which the concomitant hypertriglyceridemia accompanying low HDL may be responsible for the increased CHD risk is an issue that has not been completely settled. Austin [20] has suggested that although there is a highly significant univariate relationship between triglyceride concentration and CHD, but most of the time, there is no residual association between triglyceride levels and CHD risk, once the concomitant variation in HDL-cholesterol is considered. Therefore, there has been a major debate in the field of epidemiology as to whether or not hypertriglyceridemia is an independent risk factor for CHD [44,45]. This controversy has had, however, a negative impact on the proper interpretation of hypertriglyceridemia by clinicians by confusing many of them. As there appears to be a consensus from epidemiological studies that fasting triglycerides may be at best a weak independent correlate of CHD risk [19,20], some clinicians have failed to recognize the importance of hypertriglyceridemia as a marker of a cluster of atherothrombotic abnormalities increasing risk of CHD.

Another approach to deal with this issue has been to stratify subjects on the basis of triglyceride and HDL-cholesterol levels (i.e. treat these as categorical variables) rather than using the conventional multivariate analysis approach in which these lipids are viewed as continuous variables [13,18,45–47]. In the Helsinki heart study [46] in which subjects were randomized to a placebo or to gemfibrozil for five years, it was found in the placebo group that the highest risk of cardiac events was found among subjects who were characterized by both triglyceride levels above 2.3 mmol/l and by HDL-cholesterol concentrations below 1.08 mmol/l. In this study, lowest HDL-cholesterol concentration in the absence of hypertriglyceridemia was not associated with a substantial increase risk of coronary events [46]. In the PROCAM study [13] in which a sample of 4559 men were followed for a period of six years, the greatest incidence of CHD was found in the subgroup of men who were characterized by both increased triglyceride concentrations (above 2.3 mmol/l) and reduced HDL-cholesterol levels (below 0.9 mmol/l). More recently, the Copenhagen male study [47] has provided additional evidence that the high triglyceride-low HDL-cholesterol dyslipidemia was associated with a substantial increase in the risk of CHD. In this study, in which a sample of 2906 men were followed over eight years, the incidence of CHD reached 6.6% in subjects who were 'normolipidemic' by their criteria. Subjects in the 5th quintile of LDL cholesterol levels were characterized by an 8.2% incidence of CHD. However, men who were both in the top tertile of the fasting triglyceride distribution and in the lowest tertile of HDL-cholesterol levels were characterized by an 11.4% incidence of CHD, indicating that this dyslipidemia was associated with a greater risk of CHD than isolated raised LDL-cholesterol levels. In addition, an increase of 20% in LDL-cholesterol levels among men of the Copenhagen male study was associated with a 1.15 relative risk of CHD. However, a 20% increase in the cholesterol/HDL-cholesterol ratio was associated with a 1.26 relative risk of CHD, this variable being the best predictor of CHD risk in this cohort. Therefore, there is increasing evidence suggesting that the high triglyceride-low HDL-cholesterol dyslipidemia is associated with a substantially increased risk of CHD and that the risk associated with this condition is probably greater than raised LDL-cholesterol alone. Furthermore, the high triglyceride-low HDL-cholesterol dyslipidemia is the most prevalent atherogenic phenotype [48,49] which emphasizes that proper screening and treatment of this condition would have a greater impact on the incidence of CHD in our population than treating patients with raised LDL-cholesterol levels.

3. The low HDL syndrome: the Québec cardiovascular study

The following section describes the evidence from the Québec cardiovascular study that the low HDL syndrome is associated with a substantially increased risk of IHD. In 1985, we had the opportunity to study a sample of 2443 middle-aged men for their IHD risk factors, including the measurement of a fasting lipoprotein-lipid profile. Subjects with IHD or with triglyceride levels greater than 4.5 mmol/l were excluded from follow-up. We were then able to obtain 5-year follow-up data in a sample of 2103 men without IHD. Over this period, 114 men developed clinical signs of IHD whereas 1989 remained free from these clinical manifestations [50]. Subjects' baseline characteristics are presented in Table 1. Whereas there was no difference in body mass index nor in fasting leptin concentration (a marker of body composition and of total body fat content) between the two groups, subjects who developed IHD were three years older, had a higher systolic blood pressure, a higher prevalence of diabetes mellitus and of tobacco smoking. As expected, men with events had higher cholesterol, LDL-cholesterol and triglyceride levels as well as reduced HDL-cholesterol concentration. With IHD, subjects also had higher apo B concentration (a marker of the concentration of atherogenic lipoproteins [VLDL + IDL + LDL]) and almost a

Table 1
Characteristics of the 114 men of the Québec cardiovascular study who developed IHD compared to the sample of 1989 men who remained IHD-free over the 5-year follow-up

Variable	IHD (−), $n = 1989$	IHD (+), $n = 114$	P value
Age (years)	56 ± 7	59 ± 8	<0.0001
Body mass index (kg/m^2)	26 ± 4	27 ± 4	NS
Leptin[a] (mg/ml)	5.56 ± 3.12	5.36 ± 2.90	NS
Diabetes (%)	4	16	<0.0001
Smokers (%)	34	44	0.07
Systolic blood pressure (mmHg)	130 ± 17	137 ± 17	<0.0001
Diastolic blood pressure (mmHg)	81 ± 10	82 ± 12	0.47
Triglycerides (mmol/l)	1.74 ± 0.75	2.00 ± 0.74	<0.0001
Cholesterol (mmol/l)	5.7 ± 1.0	6.1 ± 1.0	<0.0001
LDL-cholesterol (mmol/l)	3.9 ± 0.9	4.2 ± 1.0	<0.0001
HDL-cholesterol (mmol/l)	1.04 ± 0.26	0.96 ± 0.24	<0.0001
Apolipoprotein B (mg/dl)	1.16 ± 0.30	1.30 ± 0.32	<0.0001
Cholesterol/HDL-cholesterol ratio	5.8 ± 1.7	6.7 ± 1.9	<0.0001

[a] In a case-control analysis, leptin was measured in 86 IHD men and in 95 men who remained IHD-free and who were matched for body mass index, diabetes, smoking and medication use.

one unit difference in the cholesterol/HDL-cholesterol ratio.

Table 2 illustrates the relative risk of IHD associated with a 10% change in various risk variables as estimated by Cox proportional hazards univariate models. We found that an increase of 10% in blood pressure was associated with a 32% increase in IHD risk. While increased body mass index had no impact on IHD risk, an increased LDL-cholesterol concentration of 10% was associated with a 15% increase in the risk of IHD. Furthermore, a 10% increase in apo B also increased IHD risk by 17%. In univariate analysis, and in concordance with previous reports from other prospective studies [20,44], we found a significant relationship between fasting triglyceride concentration and IHD risk, a 10% elevation in triglyceride concentrations being associated with a 7% increase in IHD risk. Finally, a 10% reduction in HDL-cholesterol levels was associated with a 13% increase in IHD risk.

We then performed multivariate stepwise analyses using the Cox proportional hazards model to identify the best independent predictors of IHD using conventional risk and lipid variables in our cohort of men (Table 3). We found that diabetes, LDL-cholesterol, smoking, age, systolic blood pressure, HDL-cholesterol and medication use (which mainly included beta blockers and diuretics) were the best independent predictors of IHD in this sample of middle-aged men. These results are fully concordant with other prospective studies and suggest that men of the Québec cardiovascular study globally 'behaved', from a risk factor standpoint, like other cohorts of men such as the Framingham, Helsinki and PROCAM studies [12,13,18,22,46]. However, when we computed the cholesterol/HDL-cholesterol ratio, it became the best single lipid predictor of IHD [28]. These results suggest that the risk associated with the high triglyceride-low HDL-cholesterol dyslipidemia could probably be most appropriately assessed with the cholesterol/HDL-cholesterol ratio.

Therefore, it was important to examine the relationship of HDL-cholesterol and LDL-cholesterol to the cholesterol/HDL-cholesterol ratio in our cohort (Fig. 3). Although there was a significant positive correlation between LDL-cholesterol and the cholesterol/HDL-cholesterol ratio, the shared variance only reached 32% whereas a larger proportion of the variance in this ratio was explained by HDL-cholesterol levels (61%). Furthermore, the relationship appeared to be curvilinear, suggesting that further reduction in HDL-cholesterol to low concentrations may have a greater impact on the cholesterol/HDL-cholesterol ratio and concurrently on the risk of IHD. These results emphasize HDL-cholesterol as a potent modulator of the cholesterol/HDL-cholesterol ratio. The impact of a reduced HDL-cholesterol concentration on an increased cholesterol/HDL-cholesterol ratio is further emphasized in

Table 2
Non-adjusted relative risk of IHD over a 5-year period associated with a 10% change in risk factors in the Québec cardiovascular study[a]

Variable (10% change)	RR of IHD (95% CI)
Age (57–62 years)[b]	35% (17%; 55%)
Systolic blood pressure (130–143 mmHg)	32% (16%; 50%)
Body mass index (26–29 kg/m^2)	12% (−1%; 26%)
LDL-cholesterol (3.9–4.3 mmol/l)	15% (7%; 24%)
Apolipoprotein B (117–129 mg/dl)	17% (10%; 25%)
Triglycerides (1.7–1.9 mmol/l)	7% (4%; 11%)
HDL-cholesterol (1.0–0.9 mmol/l)	13% (4%; 23%)

[a] RR: Relative risk; CI: Confidence interval.
[b] Each of these values represent a 10% increase or decrease from the mean value in the cohort.

Table 3
Multivariate stepwise analysis[b] of risk factors in the Québec cardiovascular study[c,a]

Variable	Wald $\chi 2$	P value
Diabetes	25.0	<0.001
LDL-cholesterol	20.7	<0.001
Smoking	11.6	<0.001
Age	8.2	0.004
Systolic blood pressure	6.1	0.01
HDL-cholesterol	5.4	0.02
Medication use	4.8	0.03

[a] Variables entered in the model: diabetes, LDL-cholesterol, smoking, age, systolic blood pressure, HDL-cholesterol, triglycerides, medication use, family history of IHD.
[b] Cox proportional hazards.
[c] Excluded men with triglycerides >4.5 mmol/l.

Fig. 4 which presents the odds ratio of having a cholesterol/HDL-cholesterol ratio > 6 across quartiles of LDL or HDL-cholesterol levels among men of the Québec cardiovascular study. Being in the upper LDL-cholesterol quartile was associated with 14.4-fold increase in the odds of having an elevated cholesterol/HDL-cholesterol ratio (ratio > 6) compared to being in the first LDL quartile. Being in the first HDL-cholesterol quartile was, however, associated with a remarkable 156-fold increase in the odds ratio of having a cholesterol/HDL-cholesterol ratio > 6. These results clearly emphasize the importance of reduced HDL-cholesterol as opposed to raised LDL-cholesterol as a major factor responsible for an elevated cholesterol/HDL-cholesterol ratio in our population.

Fig. 5 shows the actual cholesterol/HDL-cholesterol ratio values among subjects stratified into tertiles of HDL-cholesterol and LDL-cholesterol. Among subjects in the upper HDL-cholesterol tertile, being also in the upper LDL-cholesterol tertile was associated with a cholesterol/HDL-cholesterol ratio of 5.2. However, among subjects with low LDL-cholesterol levels (in the first tertile), being also in the lowest HDL-cholesterol tertile were associated with a cholesterol/HDL-cholesterol ratio of 6.2. Finally, being both in the lowest HDL-cholesterol tertile and in the highest LDL-cholesterol tertile was associated with the highest cholesterol/HDL-cholesterol ratio, the average value reaching 8.6.

Fig. 6 presents the risk of IHD over a 5-year follow-up among subjects stratified on the basis of HDL-cholesterol and LDL-cholesterol tertiles. Among subjects in the upper HDL-cholesterol tertile, being in the upper LDL-cholesterol tertile was not associated with a significant increase in the risk of IHD. Being in the lowest LDL-cholesterol tertile while also being in the lowest HDL-cholesterol tertile was not associated with a significant increase risk of IHD. However, the combination of low HDL-cholesterol (first tertile) with either moderate or high LDL-cholesterol levels (second and third tertiles) was associated with a significant 3.4–3.5-fold increase in the risk of IHD.

Fig. 7 shows the odds ratios of IHD across subgroups of men classified on the basis of baseline levels of fasting triglycerides and of the cholesterol/HDL-cholesterol ratio. Both elevated triglyceride levels and an increased cholesterol/HDL-cholesterol ratio contributed to IHD risk. However, we need to keep in mind that the biological variability of a fasting triglyceride measurement (that is variation from one day to another) is notoriously greater than for HDL-cholesterol, the latter being a major contributor of the variation in the cholesterol/HDL-cholesterol ratio [20]. Thus, because we have only obtained a fasting blood sample on one occasion, it is likely that a greater proportion of subjects were misclassified for hypertriglyceridemia than for low HDL-cholesterol, as a low HDL could be seen as a more stable marker of an impaired metabolism of triglyceride-rich lipoproteins than fasting triglycerides [51]. What appears to be clear however is that a high triglyceride-low HDL-cholesterol dyslipidemia associated with an elevated cholesterol/HDL-cholesterol ratio is a prevalent and atherogenic lipoprotein phenotype (4.0 fold increase in the risk of

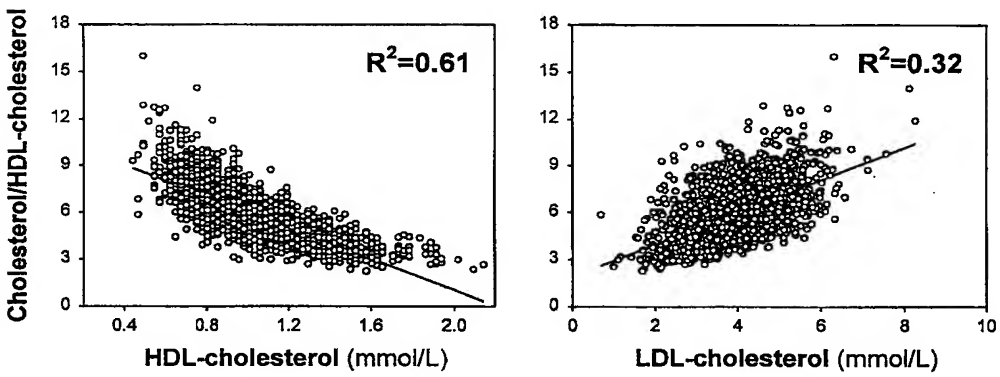

Fig. 3. Relationship between the cholesterol/HDL-cholesterol ratio and plasma HDL-cholesterol or LDL-cholesterol in men of the Québec cardiovascular study.

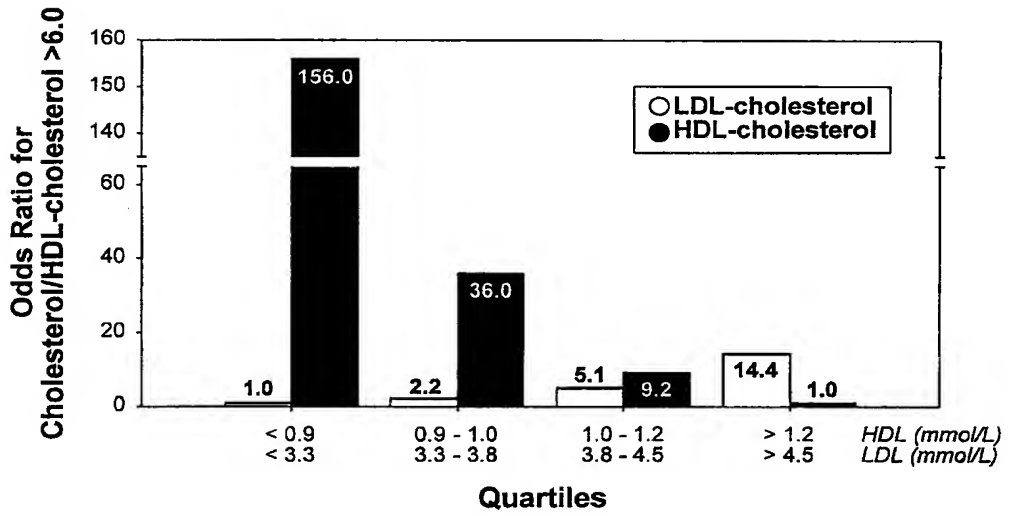

Fig. 4. Odds ratio of being characterized by a cholesterol/HDL-cholesterol ratio > 6 among men of the Québec cardiovascular study stratified into quartiles of LDL-cholesterol or HDL-cholesterol. Numbers above or within bars indicate the "fold" increases in relative risk of having a cholesterol/HDL-cholesterol ratio > 6 compared to the first quartile.

IHD in men with triglyceride levels above the 50th percentile and in the top cholesterol/HDL-cholesterol tertile) which is frequently the consequence of abdominal obesity and insulin resistance, with or without the presence of Type 2 diabetes [52]. This issue will be discussed in the next section.

3.1. Hypertriglyceridemia-low HDL-cholesterol: a prevalent atherogenic dyslipidemia among abdominally obese insulin resistant patients

As previously shown in Fig. 2, low HDL-cholesterol levels are frequently accompanied by hypertriglyceridemia although there is considerable heterogeneity among subjects showing comparable reductions in HDL-cholesterol levels. In other words, some subjects with low HDL-cholesterol levels have relatively low triglyceride concentrations whereas others are characterized by increased triglyceride levels. We have previously shown that low HDL-cholesterol concentration in the presence of triglyceride levels that are not elevated (less than about 1.35 ± 0.45 mmol/l which is commonly referred to as isolated low HDL-cholesterol) is a condition that is not associated with hyperinsulinemia, nor with the features of the insulin resistance syndrome [53]. Furthermore, we reported that it is the combination of high triglyceride (≥ 2.0 mmol/l, a value giving us the best sensitivity/specificity to identify subjects with the small, dense LDL phenotype [54])-low HDL-cholesterol which is associated with hyperinsulinemia both in the fasting state and following a 75 g oral glucose load [53], suggesting that it was the high triglyceride-low HDL-cholesterol dyslipidemia which was associated with features of the insulin resistance syndrome. More recently, we have studied postprandial lipemia in two groups of subjects showing both low HDL-cholesterol levels in the absence (> 2.0 mmol/l) or presence of hypertriglyceridemia (≥ 2.0 mmol/l) and we found no evidence of postprandial hyperlipidemia among subjects with isolated low HDL-cholesterol [55]. However, the combination of high triglyceride-low HDL-cholesterol was clearly associated with an impaired postprandial lipemia [55]. These results provide further support to the notion that the high triglyceride-low HDL-cholesterol dyslipidemia is a metabolic phenotype that is distinct from the isolated low HDL-cholesterol. We have also examined the contribution of abdominal obesity, particularly of excess visceral adipose tissue accumulation, to the high triglyceride-low HDL-cholesterol dyslipidemia [56]. We reported that excess abdominal visceral adipose tissue accumulation was associated with a marked reduction in HDL-cholesterol levels but that this low HDL-cholesterol dyslipidemia was also

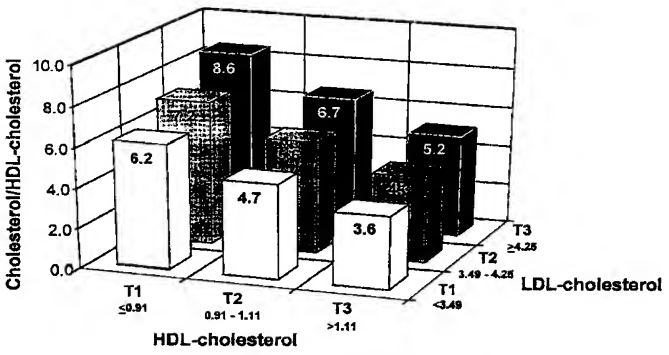

Fig. 5. Cholesterol/HDL-cholesterol ratio values among men of the Québec cardiovascular study stratified into tertiles of LDL-cholesterol and HDL-cholesterol. Numbers within bars represent total/HDL-cholesterol values.

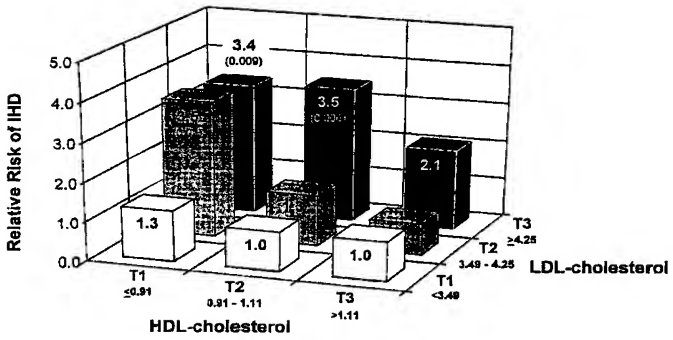

Fig. 6. Relative risk of IHD over a 5-year follow-up period among men of the Québec cardiovascular study stratified into tertiles of LDL-cholesterol and HDL-cholesterol. Numbers above or within bars indicate the "fold" relative risk compared to the first tertile of LDL-cholesterol combined to the third tertile of HDL-cholesterol. *P* values were indicated in parentheses.

accompanied by hypertriglyceridemia, elevated apo B levels, insulin resistance and hyperinsulinemia [56]. Furthermore, visceral obesity has been associated with an exaggerated triglyceride response to a high fat meal and with the postprandial accumulation of atherogenic small triglyceride-rich lipoprotein and chylomicron remnants [57].

Thus, metabolic studies that we have conducted over the last 10 years have shown that the dyslipidemia of abdominal visceral obesity is characterized by a marked reduction in HDL-cholesterol levels, normal or moderately elevated total cholesterol levels, elevation in triglyceride and apo B concentrations, an increased proportion of small, dense LDL particles, a substantial increase in the cholesterol/HDL-cholesterol ratio and by hyperinsulinemia resulting from an insulin resistant state. Furthermore, an increased susceptibility to thrombosis and a reduced fibrinolytic capacity [58–60] as well as an impaired endothelial function has been reported among insulin resistant subjects with the atherogenic dyslipidemia of abdominal obesity. Finally, it has been suggested that the small, dense cholesteryl ester depleted LDL particles which are features of visceral obesity are more susceptible to oxidation [61,62]. Therefore, this cluster of atherothrombotic abnormalities found in abdominally obese subjects with the high triglyceride-low HDL-cholesterol could contribute to substantially increase the risk of CHD and explain, to a large extent, the high CHD risk associated with the high triglyceride-low HDL-cholesterol dyslipidemia reported in several prospective studies.

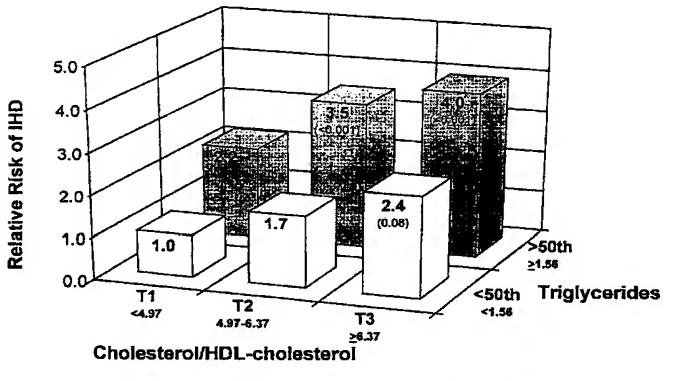

Fig. 7. Relative risk of IHD over a 5-year follow-up period among men of the Québec cardiovascular study stratified into tertiles of the cholesterol/HDL-cholesterol ratio and the 50th percentile of fasting triglyceride levels. Numbers within bars indicate the "fold" relative risk compared to the first tertile of cholesterol/HDL-cholesterol ratio combined with low triglyceride levels. *P* values were indicated in parentheses.

In this regard, we have been interested in quantifying the risk of IHD which could be related to the insulin resistance dyslipidemic syndrome. In non-diabetic men of the Québec cardiovascular study, we found that hyperinsulinemia was an independent risk factor for IHD and that the presence of both hyperinsulinemia and elevated apo B concentration was associated with a 10-fold increase in the risk of IHD [34]. As these subjects are characterized by low HDL and high triglyceride levels, we also compared the ability of the high triglyceride-low HDL-cholesterol dyslipidemia to predict risk of IHD as opposed to features of the insulin resistance syndrome which included hyperinsulinemia, elevated apo B levels and small, dense LDL particles [63]. We reported that men who were simultaneously above the median of fasting triglyceride distribution, above the median of the fasting LDL-cholesterol distribution and below the median of the HDL-cholesterol distribution were characterized by a 4.5-fold increase risk of IHD, a finding which is essentially concordant with previously reported studies which have quantified the CHD risk associated with the atherogenic dyslipidemia [63]. However, we found that subjects characterized by insulin and apo B levels above the median of the distribution of these variables and by LDL size values below the median of the distribution were characterized by more than a 20-fold increase in the risk of IHD [63]. This substantially elevated IHD risk remained significant (18-fold) after adjustment for the concomitant variation in LDL-cholesterol, triglycerides and HDL-cholesterol (results not shown). Therefore, these results suggest that the high risk associated with the high triglyceride-low HDL-cholesterol dyslipidemia could be mediated, at least to a very significant extent, by some clustering features of the insulin resistance syndrome which could include abdominal obesity, insulin resistance, elevated apo B and the presence of atherogenic small, dense LDL particles. Thus, in addition to the potential contribution of new metabolic markers such as hyperinsulinemia, apo B and LDL size, a low HDL-cholesterol concentration, when observed in the presence of hypertriglyceridemia, is an important marker of a cluster of atherothrombotic abnormalities.

Thus, there are several factors related to low HDL-cholesterol levels, which substantially increase the risk of CHD. First, a low HDL-cholesterol concentration associated with hypertriglyceridemia is strongly related to the insulin resistance-hyperinsulinemic syndrome. This condition may evolve to glucose intolerance and to type 2 diabetes among genetically susceptible individuals and clearly the presence of hyperglycemia will substantially exacerbate the risk of CHD among subjects with the high triglyceride-low HDL-cholesterol phenotype [64–66]. Abdominal obesity per se being a cause of insulin resistance, the increased free fatty acid flux from the portally-drained visceral adipose tissue will contribute to an overproduction of triglyceride-rich lipoproteins by the liver. The resulting hypertriglyceridemia will promote the transfer of triglycerides to HDL and LDL, leading to the formation of small, dense HDL and LDL particles. We know that in the presence of an atherogenic dyslipidemic profile, the presence of small, dense LDL particles substantially increases risk of CHD [31–33,63]. Finally, hypertriglyceridemia associated with low HDL and resulting from insulin resistance is accompanied by postprandial hyperlipidemia and by the accumulation of remnants in the postprandial phase. There is evidence suggesting that the accumulation of those remnants could substantially increase the risk of atherothrombotic events in the postprandial state [67,68].

4. Conclusion

Thus, we need to go beyond LDL-cholesterol measurement and LDL-cholesterol lowering therapy for the proper evaluation and optimal management of CHD risk. Reducing plasma triglyceride levels and raising HDL-cholesterol concentration through weight loss and healthy eating habits, increasing energy expenditure by introducing more physical activity in the patient's lifestyle (or even getting our subjects involved in regular endurance exercise programs), may contribute to improve features of the insulin resistance dyslipidemic syndrome. Finally, proper pharmacotherapy, if required, aimed at reducing triglyceride concentration and increasing HDL-cholesterol levels while trying to potentiate its effect by proper lifestyle management should be considered for the optimal prevention of CHD through a global risk management approach. In this regard, the recently published VA-HIT trial [69] clearly showed that a triglyceride lowering-HDL raising drug such as gemfibrozil can reduce CHD incidence over 5 years of pharmacotherapy in the absence of any effect on LDL-cholesterol levels. Results of this trial provide further support that we need to consider additional therapeutic targets than LDL-cholesterol. Despite these favorable results, considering the very high proportion of CHD patients showing the features of the high triglyceride-low HDL-cholesterol dyslipidemia associated with insulin resistance and abdominal obesity, it is believed that the therapeutic intervention should not be limited to the pharmacological management of the dyslipidemic state and that a multi-targeted approach could have a larger impact on the majority of CHD patients than current approaches.

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